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# Silver-Catalyzed Three-Component Coupling Reaction of Amines, 2-Isocyanobenzaldehydes, and 2,2,2-Trifluorodiazoethane and Synthesis of Trifluoromethyl-Substituted Indolo[1,2-*c*]quinazolines

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**Abstract.** A silver-catalyzed three-component coupling reaction of amines, 2-isocyanobenzaldehydes, and 2,2,2-trifluorodiazoethane has been developed. This reaction provides an efficient method for the construction of CF<sub>3</sub>-containing dihydroquinazolines. On the basis of this reaction, using trifluorodiazoethyl-substituted dihydroquinazolines as synthons, trifluoromethyl-substituted indolo[1,2-*c*]quinazolines were prepared in high yields via a TBHP/KI-mediated sequentian intramolecular cyclization and aromatization process.

Keywords: Amines; 2-Isocyanobenzaldehydes; 2,2,2-Trifluorodiazoethane; Dihydroquinazolines; Indolo[1,2-c]quinazoline

### Introduction

Incorporation of fluorine atoms or fluorinated moieties into organic molecules could significantly alter their physical, biological, and chemical properties.<sup>[1,2]</sup> These effects have led to wide application organofluorine compounds of in pharmaceutical, agrochemical, and materials sciences. Special attention has been paid to the syntheses of trifluoromethyl-containing compounds, especially trifluoromethyl-containing N-heterocycles, due to their unique properties, such as the high electronegativity, electron density, steric hindrance, and hydrophobicity.<sup>[1,2]</sup> Thus, various reagents and protocols for the trifluoromethylation of organic compounds have been developed over the past decades.<sup>[3]</sup> In this field, 2,2,2-trifluorodiazoethane (CF<sub>3</sub>CHN<sub>2</sub>) has emerged as particularly useful and versatile CF<sub>3</sub>-source in the preparation of various CF<sub>3</sub>-containing *N*-heterocycles such as pyrazolines,<sup>[4]</sup> pyrazoles,<sup>[5]</sup> triazoles,<sup>[6]</sup> tetrazoles,<sup>[7]</sup> pyridazines,<sup>[8]</sup> and imidazoles.<sup>[9]</sup> Obviously, it is of value to develop new synthetic strategies for the preparation of various new CF<sub>3</sub>-containing N-heterocycles employing 2,2,2trifluorodiazoethane as CF<sub>3</sub>-source.

Dihydroquinazolines and indolo[1,2-c]quinazolines are an important class of fused *N*-heterocycles that are widely found in natural products and synthetic compounds with a broad spectrum of biological activities.<sup>[10,11]</sup> Consequently, numerous powerful methods for the synthesis of these valuable skeletons have

been developed over the past few decades.<sup>[12,13]</sup> However, to the best of our knowledge, there are no reports on the synthesis of CF<sub>3</sub>-containing dihydroquinazolines. Although several method are available for the construction of indolo[1,2 tifluoromethyl-substituted c]quinazolines, such as cyclocarbonylation of oalkynyltrifluoroacetanilides,[14] couplingcyclization of N-(2iodophenyl)trifluoroacetimidoyl chlorides and indoles<sup>[15]</sup> and intramolecular cyclization of 2-(2amidoaryl)-1*H*-indoles,<sup>[16]</sup> transition metal catalysts are generally required. Thus, development of efficient methods for the tifluoromethyl-substituted synthesis of indolo[1,2-c] guinazolines in the absence of transition metals is highly desired. As а continuation of our studies on the applications of diazo compounds<sup>[9,17]</sup> and isocyanides,<sup>[18]</sup> herein we report a silver-catalyzed three-component reaction 2coupling of amines, isocyanobenzaldehydes, and 2,2,2trifluorodiazoethane. This reaction provides an efficient method for the construction of CF<sub>3</sub>containing dihydroquinazolines in a single step from readily available substrates under rather mild conditions. On the basis of this reaction, using CF<sub>3</sub>-containing dihydroquinazolines as synthon, trifluoromethyl-substituted indolo[1,2c]quinazolines were prepared in high yields via a TBHP/KI-mediated sequential intramolecular cyclization and aromatization process.

# **Results and Discussion**

Initially, the three-component reaction of 4methoxyaniline 1a, 2-isocyanobenzaldehyde 2a, and 2,2,2-trifluorodiazoethane 3 was investigated to optimize the reaction conditions. No desired product was observed when the reaction of 1a (0.2 mmol), **2a** (0.2 mmol) and **3a** (0.4 mmol) was performed in the absence of silver catalysts in toluene at room temperature for 12 h (Table 1, entry 1). Under catalysis of Ag<sub>2</sub>CO<sub>3</sub> (10 mol%), the three-component reaction proceeded smoothly give trifluorodiazoethyl-substituted the to dihydroquinazoline 4aa in 29% yield in the absence of 4Å molecular sieves (entry 2). To our delight, the addition of 4Å molecular sieves (100 mg) improved the yield of 4aa to 93% under otherwise identical conditions (entry 4). Decreasing the amount of Ag<sub>2</sub>CO<sub>3</sub> and the ratio of 1a/2a/3 led to lower yields (entries 3 and 5). When AgF was employed as catalyst, the desired product 4aa was obtained in 90% yield (entry 8). Other silver catalysts, such as AgOAc, AgOTf, AgO<sub>2</sub>C<sub>2</sub>F<sub>3</sub> and AgNO<sub>3</sub> were less effective than  $Ag_2CO_3$  (entries 7-10). Among the solvents tested, toluene turned out to be the best choice. Product 4aa was produced in 86% yield when the reaction was performed in THF (entry 11). When the reaction was carried out in CHCl<sub>3</sub>, only a trace amount of **4aa** was observed (TLC) (entry 12).

Table 1. Optimization of reaction conditions.[a]

$MeO \xrightarrow{NH_2} + \underbrace{CHO}_{NC} + \underbrace{N_2}^{CF_3} \underbrace{[Ag], 4\mathring{A} MS}_{solvent, rt} \xrightarrow{F_3C} \underbrace{N_2}_{N} \xrightarrow{OMe}$						
1a	1a 2a 3			4aa		
Entry	Catalyst [mol%]	Solvent	1a/2a/3	T/h	Yield <sup>[b]</sup> [%]	
1		toluene	1:1:2	12		
2	$Ag_2CO_3(10)$	toluene	1:1:2	8	29 <sup>[c]</sup>	
3	$Ag_2CO_3(5)$	toluene	1:1:2	8	79	
4	$Ag_2CO_3(10)$	toluene	1:1:2	8	93 <sup>[d]</sup>	
5	$Ag_2CO_3(10)$	toluene	1:1:1	8	45	
6	AgF(10)	toluene	1:1:2	8	90	
7	AgOAc (10)	toluene	1:1:2	8	51	
8	AgOTf(10)	toluene	1:1:2	8	47	
9	$AgO_2C_2F_3(10)$	toluene	1:1:2	8	77	
10	$AgNO_3(10)$	toluene	1:1:2	8	37	
11	$Ag_2CO_3(10)$	THF	1:1:2	8	86	
12	Ag <sub>2</sub> CO <sub>3</sub> (10)	CHCl <sub>3</sub>	1:1:2	12	trace	

<sup>[a]</sup> Reaction conditions: 1a (0.2 mmol), 2a (0.2 mmol),
 3 (0.2 or 0.4 mmol), catalyst (0.01-0.02 mmol), 4Å
 MS (100 mg), solvent (2.0 mL), at rt for 8-12 h.

- <sup>[b]</sup> Estimated by <sup>1</sup>H NMR spectroscopy using CH<sub>2</sub>Br<sub>2</sub> as an internal standard.
- <sup>[c]</sup> The reaction was performed in the absence of 4Å MS.

<sup>[d]</sup> Isolated yield.

Table 2. Reaction scope of amines. [a,b]



- (0.4 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.2 mmol), 4Å MS (100 mg), toluene (2.0 mL), at room temperature for 8-12 h.
- <sup>[b]</sup> Isolated yield.



Figure 1. X-ray crystal structure of 4ca.

With the optimal reaction conditions in hand, we investigated the substrate scope of the reaction with respect to amines 1 and the results are summarized in Table 2. Satisfyingly, the three-component reaction showed broad tolerance to amines 1. Various aromatic primary amines 1a-r, such as arylamines with electron-rich, electron-neutral, or electron-deficient groups on the aromatic ring, biphenyl-4-ylamine,  $\alpha$ - and  $\beta$ naphthylamine, and heteroaromatic amine, could react smoothly with 2-isocyanobenzaldehyde 2a and 2,2,2-trifluorodiazoethane 3 to produce the corresponding dihydroquinazolines 4a-ra in good to excellent yields. The structure of 4ca was confirmed by single-crystal X-ray crystallography (Figure 1).<sup>[19]</sup> It is noteworthy that threecomponent reaction tolerates ortho-substituted arylamines 11 and 1m, indicating that the transformation exhibits good tolerance of steric hindrance. Besides to aromatic primary amines, a range of aliphatic primary amines, such as benzylamine **1**s, 2-phenylethan-1-amine 1t, cyclohexanamine 1u, butan-1-amine 1v, hexan-1amine 1w, propan-2-amine 1x, and even including the sterically hindered tert-butylamine 1y, also proved to be efficient partners, and the desired dihydroquinazolines 4s-ya were obtained in high to excellent yields. More importantly, even in the case of using 2,2,2-trifluoroethan-1amine 1z and ethyl glycinate 1z' as nitrogen sources, the three-component reaction also worked well, yielding the desired products 4za and 4za' in 83% and 80% yields, respectively. In addition, a scale-up reaction of 1a (5.0 mmol), 2a (5.0 mmol) and 3(10 mmol) was carried out for 12 h under otherwise identical conditions as above, furnishing 1.47 g of the desired product 4aa in 85% isolated yield, showing the practicality of the transformation.

**Table 3.** Reaction scope of 2-isocyanobenzaldehydes.<sup>[a,b]</sup>



[a] Reaction conditions: 1a (0.2 mmol), 2 (0.2 mmol), 3 (0.4 mmol), Ag<sub>2</sub>CO<sub>3</sub> (0.02 mmol), 4Å MS (100 mg), toluene (2.0 mL), at room temperature for 8-12 h.
[b] Isolated yield.

Next, we turned to extend the scope of 2isocyanobenzaldehydes 2. As shown in Table 3, various 2-isocyanobenzaldehydes 2b-e bearing either electron-withdrawing or electron-donating R groups on the aromatic ring could react smoothly with 1a and 2,2,2-trifluorodiazoethane 3 to give the corresponding CF<sub>3</sub>-containing dihydroquinazolines 4ab-e in high yields (Table 3). Based on structural feature the of trifluorodiazoethyl-substituted dihydroquinazolines 4, together with the consideration of the application of carbene reaction of diazo compounds,<sup>[20]</sup> we reasoned that trifluoromethylated indolo[1,2-*c*]quinazoline derivatives can be constructed via an intramolecular C-H carbene insertion to the neighboring aryl ring. Detailed examination of the reaction conditions indicated that the

indolo[1,2-c] guinazoline **5a** could be obtained in 85% yield from trifluorodiazoethyl-substituted dihydroquinazoline 4aa (0.2 mmol) in C<sub>2</sub>H<sub>5</sub>OH (2.0 mL) in the presence of TBHP (0.4 mmol), KI (0.06 mmol) and  $C_6H_5SO_2Na$  (0.2 mmol) at 60 °C for 8 h (Table 4). In addition, we found that the reaction showed broad tolerance to various R substituents of 4. All selected substrates 4a-ca, and 4ma, bearing either electron-4e-ga withdrawing or electron-donating R groups on the aromatic rings, could efficiently undergo the cyclization-aromatization reaction to give the corresponding trifluoromethylated indolo[1,2c]quinazolines **5a-g** in good to high yields. In the case of 4na, the intramolecular cyclization also efficiently with proceeded moderate resulting in the regioselectivity, expected products 5h and 5h' in 49% and 24% yields, respectively. Obviously, the reaction provides a new strategy for highly efficient synthesis of trifluoromethylated indolo[1,2-c]quinazoline derivatives from readily available substrates under transition metal-free conditions.

**Table 4.** Synthesis of trifluoromethylated indolo[1,2-*c*]quinazolines 5.<sup>[a,b]</sup>



<sup>[4]</sup> Reaction conditions: **4** (0.2 mmol), TBHP (0.4 mmol), PhSO<sub>2</sub>Na (0.2 mmol), KI (0.06 mmol), C<sub>2</sub>H<sub>5</sub>OH (2.0 mL), at 60 °C for 8-12 h. <sup>[b]</sup> Isolated yield.



In addition, one-pot synthesis of **5a** without purification of dihydroquinozolines **4aa** was also investigated. As a result, when the three-component reaction of **1a** (0.2 mmol), **2a** (0.2 mmol), and **3** (0.4 mmol) was performed under the optimal reaction conditions for 8 h, followed by treatment with TBHP (0.4 mmol), KI (0.06 mmol), and  $C_6H_5SO_2Na$  (0.2

mmol) in ethanol (2.0 mL) at 60 °C for 8 h, indolo[1,2-c]quinazoline **5a** was obtained in 43% yield (Scheme 1).

To further probe the mechanism for the formation of **4**, the reaction of aldimine **6** with 2,2,2trifluorodiazoethane **3** was also investigated (Scheme 2). As expected, the desired product **4aa** was obtained in 84% yield under the optimal reaction conditions, which indicates aldimine **6** may be the key intermediate.



Based on the experimental results and the relevant literature,<sup>[20-24]</sup> a possible mechanism for the formation of 4 and 5 is proposed in Scheme 3. Initially, in situ condensation of amines 1 and 2isocyanobenzaldehydes 2 generates aldimine 6, which is converted into intermediate **B** via the nucleophilic addition of silver trifluorodiazoethylide A generated by the reaction of 2,2,2trifluorodiazoethane 3 with  $Ag_2CO_3$ , to aldimine 6.<sup>[21]</sup> Subsequently, intermediate **B** undergoes insertion of isonitrile into the N-Ag bond to form intermediate C,<sup>[22]</sup> followed by protonation to produce the corresponding dihydroquinazolines 4 (Scheme 3). thermal conditions, Under reactive the dihydroquinazolines 4 may undergo denitrogenation to produce carbene **D**, which undergoes a concerted C-H carbene insertion to the neighboring arene to give intermediate **E**. In addition,  $PhSO_2Na$  is oxidized by 'BuO• and 'BuOO• generated by the decomposition of TBHP in the presence of KI,<sup>[23]</sup> to produce the sulfonyl radical, which abstracts the H atom on the sp<sup>3</sup>-carbon adjacent to the nitrogen atom of intermediate **E** to give intermediate  $\mathbf{F}$ .<sup>[24]</sup> Finally, intermediate F undergoes radical hydrogen abstraction by the sulfonyl radical to give trifluoromethylated indolo[1,2-c]quinazoline 5 (Scheme 3).



Scheme 3. Proposed mechanism for the formation of 4 and 5.

## Conclusion

In conclusion, we have developed a silver-catalyzed three-component coupling reaction of amines, 2isocyanobenzaldehydes, and 2,2,2trifluorodiazoethane. This reaction provides a highly efficient method for the construction of CF<sub>3</sub>containing dihydroquinazolines in a single step from readily available substrates in good to excellent yields under mild conditions. More importantly, using trifluorodiazoethyl-substituted dihydroquinazolines as tifluoromethyl-substituted synthon, indolo[1,2c]quinazolines were prepared in high yields via . TBHP/KI-mediated sequential intramolecular cyclization and aromatization process. Further studies on the application of trifluorodiazoethyl-substituted dihydroquinazolines are ongoing.

### **Experimental Section**

# General Procedure for the Preparation of 4 (4aa as Example)

To a solution of An oven-dried vial equipped with a magnetic stir bar was charged with *p*-anisidine **1a** (24.6 mg, 0.2 mmol), 2-isocyanobenzaldehyde **2a** (26.3 mg, 0.2 mmol), Ag<sub>2</sub>CO<sub>3</sub> (5.6 mg, 10 mol%), 4A MS (100 mg), then a fresh solution of CF<sub>3</sub>CHN<sub>2</sub> **3** in toluene (0.2 M, 2.0 mL) was added. The resulting suspension was stirred at 25 °C for 8 h until **2a** disappeared. After the reaction was complete, the resulting mixture was filtered (Celite/DCM) and concentrated under a reduced pressure. The crude residue was purified by silica gel column chromatography (eluent: petroleum ether/ethyl acetate = 5/1, V/V) to afford pure product **4aa** (64.4 mg, 93%) as a yellow liquid. <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 7.37 (s, 1H), 7.35 – 7.31 (m, 1H), 7.27 – 7.23 (m, 3H), 7.23 – 7.19 (m, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 6.99 (dd, *J* = 9.6, 2.7 Hz, 2H), 5.87 (s, 1H), 3.84 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$ : 158.91, 147.26, 140.82, 135.01, 129.64, 126.35, 126.31, 126.10, 125.39, 125.27 (q, *J*<sub>CF</sub> = 269.1 Hz), 119.25, 115.22, 56.70, 55.56. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$ : -56.95. HRMS (ESI-TOF): [M + H]<sup>+</sup> calculated for C<sub>17</sub>H<sub>14</sub>F<sub>3</sub>N<sub>4</sub>O<sup>+</sup>: 347.1114, found: 347.1117.

General Procedure for the Preparation of 5 (5a as

#### Example)

Under the air atmosphere conditions, sodium benzenesulfinate (0.2 mmol, 33 mg), KI (30 mol%, 10 mg), trifluoromethylated 3,4-dihydroquinazoline diazo compound 4aa (0.2 mmol, 66 mg) and ethanol (1.0 mL) were added into a 15 mL sealed tube. Subsequently, TBHP (0.11 mL, 2.0 eq., 5.0 M in nonane) in ethanol solution (1.0 mL) was added into the suspension over 10 minutes via a syringe pump at room temperature. After completion of the addition, the reaction mixture was stirred at 60 °C for an additional 8 h, until complete consumption of **4aa** as monitored by TLC analysis. After completion of the reaction, the mixture was poured into the water and was extracted with DCM ( $3 \times 10$  mL). The organic layers were combined and dried over some surface and was the concentrated in vacuum. The resulting residue was purified by column chromatography on silica gel (eluent, petroleum ether/ethyl acetate = 5:1, V/V) to afford the product **5a** ( $5^{2}$  8 mg (85%) as a white solid. m.p. 143 - 145 °C; <sup>1</sup>H combined and dried over sodium sulfate and was then ether/ethyl acetate = 5:1, V/V) to afford the product **Sa** (53.8 mg, 85%) as a white solid. m.p. 143 – 145 °C; <sup>1</sup>H NMR (600 MHz, CDCl<sub>3</sub>)  $\delta$ : 9.00 (s, 1H), 8.40 (d, J = 8.1 Hz, 1H), 7.87 (d, J = 7.9 Hz, 1H), 7.81 (d, J = 9.0 Hz, 1H), 7.65 (t, J = 7.5 Hz, 1H), 7.60 (t, J = 7.6 Hz, 1H), 7.39 (s, 1H), 7.06 (dd, J = 9.0, 2.3 Hz, 1H), 3.91 (s, 3H). <sup>13</sup>C NMR (151 MHz, CDCl<sub>3</sub>)  $\delta$ : 157.96, 140.59, 135.81, 132.36 (q,  $J_{CF} = 4.4$  Hz), 130.38, 128.74, 128.33, 127.39 (d,  $J_{CF} = 1.5$  Hz), 125.57 (q,  $J_{CF} = 5.6$  Hz), 125.56 (q,  $J_{CF} = 267.4$  Hz), 123.87, 118.89, 114.05, 110.58, 101.56 (q,  $J_{CF} = 4.1$  Hz), 99.26 (q,  $J_{CF} = 37.0$  Hz), 55.71. <sup>19</sup>F NMR (470 MHz, CDCl<sub>3</sub>)  $\delta$ : -52.90. HRMS (ESI-TOF): [M + H]<sup>+</sup> calculated for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sup>+</sup>; 317.0896. found: 317.0892. for C<sub>17</sub>H<sub>12</sub>F<sub>3</sub>N<sub>2</sub>O<sup>+</sup>: 317.0896, found: 317.0892.

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Silver-Catalyzed Three-Component Coupling Reaction of Amines, 2-Isocyanobenzaldehydes, and 2,2,2-Trifluorodiazoethane and Synthesis of Tifluoromethyl-Substituted Indolo[1,2-c]quinazolines



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